Public Health Service
Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

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San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: 510/337-6700

VIA FEDERAL EXPRESS

Our ref: 29-53759

April 8, 1999

Dale Richardson
President and Chief Operating Officer
Fresenius Hemotechnology, Inc.
110 Mason Circle, Suite A
Concord, CA 94520

WARNING LETTER

Dear Mr. Richardson:

An inspection was conducted of your firm, Fresenius Hemotechnology, Inc., between January 6 and 13, 1999 by Investigators Eric W. Anderson and Charles D. Harris. The investigators determined during the inspection that your firm imports for domestic distribution the AS104 Cell Separator and associated Therapeutic Plasma Exchange (TPE) tubing sets. These products are medical devices as defined by Section 201(h) of the Federal Food, Drug and Cosmetic Act.

The inspection revealed that these devices are adulterated within the meaning of 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packaging, storage, or installation are not in conformance with the Quality Systems Requirements (QSRs) for medical devices as set forth in Title 21, Code of Federal Regulations (CFR) Part 820 as described below.

Your firm has had knowledge of several serious reactions and one death associated with the use of its equipment, but has not fully investigated the relationship between the devices and the incidents. Specifically:

1. Your complaint CO73, received August 26, 1998, involved a patient who, after a pheresis procedure, exhibited tea-colored urine. Your investigation attributed this to hemolysis due to kinking of the TPE set. The TPE set had been redesigned in November 1997, which resulted in a shortening of the packed cell line. Shortening the line is thought to predispose it to kinking. To date, your firm lacks empirical evidence which links this incident to cell lysis. Without such evidence, your failure investigation can neither be considered complete nor conclusive. [21 CFR 820.198(d)]

2. You have failed to establish and maintain procedures for handling and for defining events which are reportable to the Agency under the Medical Device Reporting Regulation. For instance, two similar complaints, CO42 and CO43, both involved the use of sterile water and 5% albumin in lieu of the 25% albumin which is to be used as replacement fluid during pheresis. While CO42 was reported as an MDR, CO43 was not. This disparity exemplifies the lack of consistency in your complaint and MDR handling systems due to lack of reporting criteria. [21 CFR 820.198(a)(3)]

The ASC 104 Cell Separator and Therapeutic Plasma Exchange (TPE) tubing sets are misbranded within the meaning of Section 502((t)(2) of the Act, in that adverse event files were not established and maintained, and information required to be submitted to the Food and Drug Administration by the Medical Device Reporting (MDR) regulation specified in 21 CFR Part 803 was not submitted as follows:

1. You have failed to conduct an investigation and to evaluate the cause of a reportable event that one of your marketed devices may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(b)(2). For example: complaint number CO44, which involves a death, did not contain any documentation showing that your firm investigated the incident.

2. You have failed to establish and maintain written MDR procedures, as required by 21 CFR Part 803.17. For example: Complaint Handling Procedure Revision A, dated October 1, 1998, Page 3 Paragraph 6.2 does not meet the requirements for written MDR procedures regarding internal systems, documentation, and record keeping.

3. You have not established and maintained MDR files as required by 21 CFR Part 803.18. For example: your firm does not maintain an MDR event file for reports submitted to FDA and for incidents in which a decision has been made not to submit a MDR report.

4. You have failed to report promptly to FDA certain actions concerning device correction and removal as required by 21 CFR 806.10. For example: your firm initiated a recall for the ASC104 Cell Separator and TPE tubing sets on September 11, 1998, but did not notify FDA until November 17, 1998, via facsimile.

We acknowledge receipt of the March 20, 1999 written response to the inspection, submitted by Ms. Virginia Singer, Manager of Regulatory Affairs. In that letter, some of the corrective measures being undertaken by your firm are described. The following comments are offered regarding the response letter:

Regarding Complaint CO73, Ms. Singer noted that the nurse at the user facility had initially notified Fresenius Hemotechnology of the event on August 25, 1998, the date red cells were noted in the waste plasma bag and the patient exhibited the discolored urine. However, your firm apparently did not contact the hospital for additional information until January 26, 1999, an untimely delay during which vital information was probably lost due to the lack of nursing notes in the patient's chart. Your new complaint and medical device reporting procedure appears to be very comprehensive. We will assess your adherence to this procedure during a follow-up inspection of your firm, during which time we will evaluate the timeliness for complaint investigation.

Regarding Complaint CO67, we find the documentation might have been more complete had there been documentation in the files which supported Nurse [redacted] calculations, derivations, and conclusions. This comment carries through to other complaints investigated by your staff. We will evaluate the thoroughness of your complaint investigation documentation system during our next inspection.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA483 issued to Ms. Virginia R. Singer, Manager of Regulatory Affairs and Quality Assurance, may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, requests for Certificates of Exportability and to Foreign Governments will not be cleared until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the date on which the corrections will be completed.

Your response should be sent to the following individual:

Andrea P. Scott
Compliance Officer
U. S. Food and Drug Administration
96 North Third St., Suite 325
San Jose, CA 95112

Sincerely,

Charles D. Moss
Acting District Director

for Patricia C. Ziobro
District Director
San Francisco District

Cc: Ms. Virginia Singer
Mr. Rainer Baule
Dr. Rüdiger Witt
Dr. Gerd Krick
Mr. Thomas Hergenröther